

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
15 January 2004 (15.01.2004)

PCT

(10) International Publication Number
WO 2004/004644 A3

- (51) International Patent Classification⁷: **A61K 31/44**, 31/52, 31/55
- (74) Agent: **CLARK, Paul, T.**; Clark & Elbing LLP, 101 Federal Street, Boston, MA 02110 (US).
- (21) International Application Number: PCT/US2003/020972
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (22) International Filing Date: 3 July 2003 (03.07.2003)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
60/394,029 5 July 2002 (05.07.2002) US
60/412,402 20 September 2002 (20.09.2002) US
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- (63) Related by continuation (CON) or continuation-in-part (CIP) to earlier applications:
US 60/394,029 (CIP)
Filed on 5 July 2002 (05.07.2002)
US 60/412,402 (CIP)
Filed on 20 September 2002 (20.09.2002)
- (71) Applicant (*for all designated States except US*): **BETH ISRAEL DEACONESS MEDICAL CENTER** [US/US]; 330 Brookline Avenue, Boston, MA 02215 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): **NEEL, Benjamin, G.** [US/US]; 7 Grove Street, Wayland, MA 01778 (US). **MOHI, Golam** [IN/US]; Avalon at Newton Highlands, 99 Needham Street, Newton, MA 02461 (US).
- Published:**
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*
- (88) Date of publication of the international search report:
6 May 2004
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: COMBINATION OF MTOR INHIBITOR AND A TYROSINE KINASE INHIBITOR FOR THE TREATMENT OF NEOPLASMS

(57) Abstract: The invention features methods and compositions including an mTOR inhibitor and a tyrosine kinase inhibitor for reducing the proliferation of and enhancing the apoptosis of neoplastic cells. The addition of an MEK inhibitor to this combination further enhances the effectiveness of this therapeutic method.

WO 2004/004644 A3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/20972

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/44, 31/52, 31/55

US CL : 514/291, 266, 313, 314

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/291, 266, 313, 314

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US2002/0051730 A1 (BODNAR et al) 02 May 2002 (02.05.2002), see column 14, paragraph 132.	1-3
Y		4-87
X	US 5,990,109 A (CHEN et al) 23 November 1999(23.11.1999), see claims, especially claim 38.	1-81
Y	FUKAZAWA et al., Mitogen-activated Protein/Extracellular Signal regulated Kinase Kinase (MEK) inhibitors Restore Anoikis Sensitivity in Human Breast Cancer Cell Lines with a Constitutively Activated Extracellular-regulated Kinase (ERK) Pathway, Molecular Cancer Therapeutics, American Association for Cancer Research, March 2002, Vol. 1, Pages 303-309.	7-81

☐

Further documents are listed in the continuation of Box C.

☐

See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"B" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T"

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X"

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y"

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&"

document member of the same patent family

Date of the actual completion of the international search

23 February 2004 (23.02.2004)

Date of mailing of the international search report

22 MAR 2004

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Facsimile No. (703)305-3230

Authorized officer

Nelore Bell-Harris
Mariah Seidel

Telephone No. 703-308-1123

INTERNATIONAL SEARCH REPORT

PCT/US03/20972

Continuation of B. FIELDS SEARCHED Item 3:

CAS ONLINE, CAPLUS, REGISTRY, USPATFUL

search terms: mTOR inhibitor, tyrosine kinase inhibitor, MEK, neoplasm, cancer, tumor, rapamycin